

SN 09/512,962

Docket No. S-91,732

In Response to Office Action dated May 20, 2003

## IN THE CLAIMS:

1-9 (Cancelled).

10. (Currently Amended) A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

a-(a) forming a model electron density map from known crystallographic information of [a] an exemplary model crystal structure;

b-(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

c-(c) fitting a model probability distribution function defined by

$$p(\rho_r) = \sum_k w_k \exp \left\{ -\frac{(\rho - c_k)^2}{2\sigma_k^2} \right\}$$

to the model histograms, where  $k$  is separately indexed over the protein and solvent regions of the model map.  $p(\rho_r)$  is a probability of an electron density at a point,  $w_k$  is a normalization factor,  $\rho$  is electron density,  $c_k$  is a mean value of  $\rho$ , and  $\sigma_k$  is a variance of  $\rho$ , where the fitting determines the coefficients  $w_k$ ,  $c_k$ , and  $\sigma_k$ ;

d-(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

e-(e) forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

f-(f) fitting an experimental probability distribution function defined by

$$p(\rho_r) = \sum_k w_k \exp \left\{ -\frac{(\rho - \beta c_k)^2}{2(\beta \sigma_k^2 + \sigma_{exp}^2)} \right\}$$

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to separate protein and solvent regions of the experimental histograms, where  $\beta$  is an expectation that an experimental value of  $\rho$  is less than a true value and  $\sigma_{map}$  is a variance, where the fitting determines the coefficients  $\beta$  and  $\sigma_{map}$ ;

~~g.(g)~~ determine from the experimental probability distribution function the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map from the experimental probability distribution function

$$LL(\rho(\mathbf{x}, \{\mathbf{F}_h\})) = \ln [p(\rho(\mathbf{x})|PROT) p_{PROT}(\mathbf{x}) + p(\rho(\mathbf{x})|SOLV) p_{SOLV}(\mathbf{x})]$$

where  $p_{PROT}(\mathbf{x})$  is the probability that  $\mathbf{x}$  is in the protein region and  $p(\rho(\mathbf{x})|PROT)$  is the conditional probability for  $\rho(\mathbf{x})$  given that  $\mathbf{x}$  is in the protein region, and  $p_{SOLV}(\mathbf{x})$  and  $p(\rho(\mathbf{x})|SOLV)$  are the corresponding quantities for the solvent region;

~~h.(h)~~ determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental changes to output a revised log-likelihood of any value of each experimental structure factor; [and]

~~i.(i)~~ forming from the revised log-likelihood of experimental structure factor values a new set of structure factors and returning the new set of structure factors to step (f) to iterate the process until changes to a new set of structure factors are below a predetermined value; and

(i) forming a revised experimental electron density map from the revised structure factors.

11. (Currently Amended) ~~A-The~~ method according to Claim 10, wherein step ~~a.~~ (a) further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.

12. (Currently Amended) ~~A-The~~ method according to Claim 10, wherein step ~~b.~~ (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."

13. (Currently Amended) ~~A-The~~ method according to Claim 11, wherein step ~~b.~~ (b) further includes a step of identifying protein and solvent regions by designating all

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points within a selected distance of an atom as "protein" and all other points at as  
"solvent."

14. (Currently Amended) ~~A~~The method according to Claim 10, wherein step ~~h~~  
(h) includes steps of forming a Taylor's series expansion of the log-likelihood of the  
experimental electron density map and evaluating terms of the Taylor's series  
expansion using a Fast Fourier Transform.